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Frontal lobe functions in schizophrenia : Interest of the Stuss approach.

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Abstract

Objective: The term *Executive Functions* (EFs) refers to the higher-level skills we use every day to control and coordinate our cognitive abilities and behaviours. EFs are mainly supported by the frontal lobes and its connections. EFs are frequently impaired in schizophrenia, but the profiles of executive deficits accompanying schizophrenia remains unclear. The use of specific EFs models might help to shed new light on this issue. Stuss (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017) proposed an integrative and operant model of EFs which has never been used to explore and characterize deficits in schizophrenia.

The aim of this study is to further examine EFs in schizophrenia in the light of the frontal lobe functional approach developed by Stuss (2008, 2011, 2017) in order to question EFs impairment homogeneity and heterogeneity in schizophrenia.

Methods: Forty-five patients with schizophrenia and fifty-five healthy controls were recruited. They all completed a series of neuropsychological tests selected and adapted to measure the five majors' functions of the frontal lobe described by Stuss (2017).

Results: Patients showed deficits in almost all the frontal functions. Inside each frontal lobe function, correlations were observed between all the corresponding measures. The study of profiles highlighted a heterogeneous functioning in schizophrenia.

Conclusions: The model of Stuss (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017) allows accurate and specific measures of the frontal functions and observation. Beyond “cold” or “hot” EFs division, this integrative approach is helpful to understand links within neurocognition.

Keywords:

Frontal lobe functions, executive functions, Stuss' model, schizophrenia.

1. Introduction

In schizophrenia, the activity of the prefrontal cortex (PFC) and of its circuits can be widely disturbed (Minzenberg et al., 2009; Orellana & Slachevsky, 2013; Riehemann et al., 2001; Wagner et al., 2015). Deficits of the functions related to the PFC circuitry - Executive Functions (EFs) - play a central role in cognitive and behavioural dysfunctions in schizophrenia (Snitz, et al., 2006; Snyder, et al., 2015). EFs are involved in all situations to control and coordinate our other cognitive abilities and behaviours, and comprise processes such as planning, inhibiting, controlling, shifting and updating. As summarized by Allain et al. (2019), these functions are involved in any pattern of non-routine actions. EFs incorporate both cognitive and affective dimension (Besnard et al., 2018; Chan et al., 2008). Cognitive executive skills (or “cold” EFs) do not tend to involve emotional arousal and are “mechanistic” or “logically” based (Chan et al., 2008). Emotional factors of EFs (or “hot” EFs) refer to the socio-emotional domain and are mostly evoked in motivationally and emotionally meaningful contexts (Chan et al., 2008). From a neuroanatomical point of view, cold EFs are related to dorsolateral PFC and hot EFs are associated with the activity of the orbitofrontal and ventromedial PFC (Ruiz-Castañeda et al., 2020).

In schizophrenia, cold EFs deficits have been extensively studied (Sheffield et al., 2018; Salehinejad et al., 2021). Raffard and Bayard (2012) have shown that cold executive performances in schizophrenia patients were more heterogeneous than in healthy controls, with patients exhibiting impairment in one, two, three or four executive tasks, while only six percent of patients had normal executive profile. According to Ruiz-Castañeda et al. (2020), studies focusing on hot EFs are much scarcer with contradictory results in some of them (Peyroux et al., 2019). The few clustering based approaches performed in schizophrenia have identified different profiles of sociocognitive impairments in patients with schizophrenia, with individuals showing low, medium or high level of sociocognitive functioning (Etchepare et al., 2019; Rocca et al., 2016).

From our point of view, it is insufficiently clear to what extent EFs deficits are homogeneous or heterogeneous in schizophrenia patients. Indeed, the majority of studies were based on theoretical models that only consider one or two facets of executive functioning (cold or/and hot EFs). This type

of approach gives a too restrictive vision of the role of the frontal lobes. The use of multidimensional models might help to shed new light on this issue. Moreover, the use of statistical methodology involving person-centered analysis is better suited to identify groups of individuals with schizophrenia who share common characteristics and heterogeneity within these groups (Wang & Hanges, 2011).

Among the several influential multidimensional models of EFs in literature, there is the model developed by Stuss (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017). They proposed that there is no single frontal executive or superior attentional system. They rather proposed, many different frontal systems interacting amongst themselves and other regions of the brain in shifting networks (Alexander et al., 2019). The first function concerns the regulation of energy called Energization and is associated with the superior medial PFC (SMPFC) activity. It allows both the initiative and the maintenance of a response. According to Henri-Bhargava et al. (2018) extensive damage to the SMPFC result in abulia, apathy, or akinetic mutism. Less extensive damage makes patients slow to initiate and sustain mental processes. These authors observed a slowness in tests, from reaction time to “fluency” generation ones. The second and third functions correspond to the two processes that fit the definition of cold EFs: Task setting (planning) and Monitoring. Task setting refers to developing and implementing a plan to carry out sequential activities (going to the restaurant). According to Stuss and Alexander (2007), EFs Task setting impairments are associated with lesions in the left lateral PFC (left LPFC) and are revealed by errors due to difficulty in determining response criteria. For them, the Stroop task would not measure inhibition, which would be an “inexistent” process, it would rather measure Task setting EFs by taking into account the number of errors. EFs Monitoring is the process of checking that one remains on task over time, with adjustments in behaviour as required for successful completion. Deficits in EFs Monitoring are associated with lesions of the right lateral PFC (right LPFC), and cause symptoms such as variability in a timed tapping task and inconsistency in response over the Wisconsin Card Sorting Test (WCST) (Stuss et Alexander, 2007; Stuss, 2008). The fourth function corresponds to emotional processing and behavioural regulation called Behavioural/Emotional self-regulatory functions (B/E self-functions). Ventromedial (orbitofrontal) PFC (VMPFC) is held to be involved in this function. Patients with lesions to this area have difficulty in understanding the emotional consequences of their behaviour (Bechara, et al., 2005; Stuss,

2008). Tasks sensitive to damage in this region are decision-making task such as the Gambling Tasks. The last major function of the model is related to the activity of the frontopolar regions. These regions are held to be critical for metacognitive aspects of human behaviour, such as auto-noetic consciousness, theory of mind (ToM), empathy, self-awareness, humour appreciation, and personality (Stuss, 2008). Metacognitive functions can be explored through ToM tasks. Damage to the frontal poles causes impairment of metacognitive processes, including self-awareness and ToM deficits (Henri-Bhargava et al., 2018).

While this integrative approach was used with success to study homogeneity and heterogeneity of EFs in normal ageing of EFs (Calso et al., 2016), it has not yet been applied to schizophrenia. The aim of this study is to examine EFs deficits in schizophrenia in the light of the frontal lobe functions approach developed by Stuss (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017). We used cluster analysis to identify and compare the EFs profiles in our sample of patients with schizophrenia and healthy controls and characterized each of the identified profiles. With regard to past findings, we concluded that some patients with schizophrenia are characterized by generalized EFs impairments, whereas others have difficulties with specific EFs skills and may even have no impairments at all.

2. Methods

2.1. Subjects

Forty-eight patients aged between 18 and 55 years were recruited (see table 1). All of them had to have a diagnosis of spectrum of schizophrenia according to the DSM-5 criteria (American Psychiatric Association, 2013) in relation to the medical file and confirmed by The Mini-International Neuropsychiatric Interview (MINI; Lecrubier et al., 1998). The symptomatology (clinical assessment) had to be stable during the month prior to inclusion. Participants had to be free of addiction to cannabis, alcohol, or other substances (> 2 / week), neurological disorders of vascular, infectious or neurodegenerative origin and not have participated simultaneously in a remediation program targeting neurocognitive deficits. The distribution of drug treatments among the patients was as follows: 80.0% atypical neuroleptics (e.g. risperidone, haloperidol), 42.2% of neuroleptics (e.g. cyamemazine, haloperidol), 33.3% of antidepressants (e.g. paroxetine, sertraline), 33.3% of anxiolytics (e.g.

diazepam, prazepam), 8.9% of mood stabilizing (e.g. valpromide, sodium divalproate), 6.7% hypnotics (e.g. zopiclone). Psychotropic treatment had to remain the same in the month prior to inclusion. In the wake of verbal understanding difficulties, three patients were excluded. Patients were matched with 55 healthy controls recruited from the general population (see table 1) without psychiatric disorders (controlled with the MIND).

2.2. Procedures

Participation was proposed to patients from “Réseau Rehab” of the Hospital of Niort (France) and the “C2RL” department of the Esquirol Hospital of Limoges (France). Controls were recruited in the general population on a voluntary basis in the Hospital of Niort and local newspaper reports. Both groups were subject to the same process. Data were collected in one or two sessions for controls and two or three for patients (spread over a maximum of one month). Ethical approval was obtained from the South-Mediterranean-III Ethical Committee N°IDRCB: 2017-A02984-49. ClinicalTrials.gov ID: NCT03801551. All participants provided written informed consent.

2.3. Demography measures

The French adaptation of the National Adult Reading Test (f-NART; Mackinnon & Mulligan, 2005) was used to estimate the premorbid intelligence (table 1). This test provides an estimate of the total premorbid Intelligence Quotient (pIQ). Several professional categories were described across the sample (table 1).

2.4. The frontal lobe functions measures

Following Stuss’ model (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017) and recommendations, a series of neuropsychological tests were selected and adapted to measure five major functions of frontal lobe.

2.4.1. Energization

A Phonemic Verbal Fluency task (Godefroy & GREFEX, 2008) was used to measure Energization. Participants were asked to give the greatest number of words starting with a given letter (P) for two minutes. Patients with an Energization deficit show a slowdown in their performance. Following Stuss' recommendations (Stuss, 2008), we measured the total of words produced in the first 15 seconds (VFT_15), in 2 minutes (VFT), and the difference between the number of words given in the first 15 seconds and the number of words given from 15 seconds to 60 seconds (VF60_15).

2.4.2. Executive functions

Task setting

EFs Task setting was measured by means of a Stroop task (Godefroy & GREFEX, 2008), along the lines of the variant of Stroop task used by Stuss and Alexander (2007). This task is composed of three sheets of paper of 100 items and three conditions. Participants were asked to name the colour (CN), read the words (RW) and name ink colour of the words (ICN), line by line on each sheet as quickly and accurately as possible. The Time (StroopTPS) and the number of Uncorrected Errors (StroopUE) were collected in INC minus the uncorrected errors and time in CN to measure the ability to control cognitive operation under condition of conflicting possible responses. More time and/or higher numbers of Errors means a poorer performance.

Monitoring

To measure EFs Monitoring, the 64 cards Wisconsin Card Sorting Test developed by Heaton (WCST; 1981) was administered, with explicit instructions about task parameter to approximate the version used by Stuss and Alexander (2007). Participants match the cards according to criteria. Following Stuss (2008), the 3 sorting criteria, namely shape, colour and number were given at the beginning of the task and the participants were asked to start with the "colour" criterion. Subjects should also be informed that the criteria would change after 10 consecutive passes. The measurements were obtained by recording the number of Set Loss (WCST_SL; number of changes after 3 or more consecutive successes in the same category), the number of Categories Achieved (WCST_CA; the higher the

result, the better the performance is), and the number of Total Errors (WCST_TE; the higher the result, the poorer the performance is).

2.4.3. Behavioural/Emotional Self-regulatory functions

The Iowa Gambling Task (IGT; Bechara et al., 2005) was used to assess self-regulation of behaviour and emotions. In this task, the participant is requested to draw from a deck of cards of his choice (A, B, C, D). Decks differ in function of the distribution of rewarding and punishing outcomes: A and B are “disadvantageous” decks, they involve high immediate gains but even high penalties. C and D are “advantageous”, they involve low immediate gains and occasionally low penalties. Performance score was measured by the IGT Net Score (IGT_NS) which is the total from the comparison of card choices from advantageous decks and disadvantageous decks $[(C+D)-(A+B)]$. There is a measure for every 20 cards drawn until 100 cards so 5 blocks of measures respectively called: IGT_20, IGT_40, IGT_60, IGT_80 and IGT_100.

2.4.4. Metacognitive functions

The Faux Pas Recognition Test (Stone et al., 1998) was used to assess affective and cognitive ToM, a main Metacognitive function. It consists of 20 short stories read out loud by the interviewer, 10 of which present a social misstep “faux-pas” (in these stories, a character commits an awkwardness that it would be better not to say). The measure was done on each question with faux pas: Total Score Faux Pas /60 corresponding to Global ToM Score of questions 2 to 6 (FauxPasGS), False-belief score /10 corresponding to ToM Cognitive Score of questions 5 (FauxPasCS) and Empathy score/10 corresponding to ToM Affective Score of question 6 (FauxPasAS). To ensure a general level of understanding of the stories, a last control questions /40 measure the Understanding Score (FauxPasUS) but not belong to the model. For this question, in regard to normalisation of Faux Pas by Boutantin et al. (2010), the understanding score in general population were compromised between 37 to 40 (centile 5=38). For all, the higher the score, the better the performance.

2.5. Data analysis

Results were analysed using Python. Statistics analysis were performed using “pandas”, “numpy”, “scipy”, “statsmodels” and “scikit-learn” libraries and data visualisation was obtained using “seaborn” and “matplotlib” libraries. Prior further analysis, validity of the data was assessed to determine its normality and homogeneity. The Shapiro-Wilk test was used to evaluate each variable for normality and Levene test to check the homogeneity (table S1 and S2, Figure S1). Depending if the data distribution was normal or not, Student t-test and Mann–Whitney U test were performed respectively to compare means of the different scores between patients with schizophrenia and controls. The alpha level was set at 0.05. However, since 18 variables were used, we performed a Bonferroni correction for multiple comparisons and the adjusted alpha value was 0.0028 (i.e., 0.05 divided by 18). The effect size was estimated with Cohen's d or the correlation coefficient r and classified as small ($d = 0.2$ or $r = 0.1$), medium ($d = 0.5$ or $r = 0.3$), or large ($d \geq 0.8$ or $r \geq 0.5$) (Rosenthal & Rosnow, 1984). Factor analysis was performed on the global population (controls and patients) to determine if we could identify, the five components of the frontal lobe functions approach proposed by Stuss and Alexander (2007). The number of components was set to five, and factor analysis was performed using Varimax as rotation method to maximize loading dispersion between factors. Loadings were then visualized using heatmap where cool colours indicate negative loadings and warm colours indicate positive loadings (Figure 1, table S5). Spearman correlation was used for all correlation analyses. Clustering of the patients was performed using K-mean clustering. Prior clustering, the number of three clusters was determined using dendrogram and elbow curve methods (Figures S2 and S3). In each cluster, mean of z-scores were calculated for the 5 frontal functions. Energization z-score is the mean of VF0_15 and VFT z-scores. EFs Monitoring z-score is the mean of WCST_CA, WCST_SL and WCST_TE z-scores. EFs Task setting z-score is the mean of StroopUE and StroopTPS z-scores. Metacognitive functions z-score is the mean of FauxPasGS, FauxPasCS and FauxPasAS z-scores. B/E Self-functions z-score is the mean of IGT_60 and IGT_80 z-scores.

3. Result

3.1. Demographic and clinical variables

As described in table 1, between both groups, there was no difference in age and premorbid intellectual quotient as estimated by the French adaptation of the f-NART (Mackinnon & Mulligan, 2005). There were differences between groups for gender, level of education and for repartition in professional category. The presence of an interaction was observed only on gender and WCST_CA ($F(1,43) = 4.54, p < .01$) and with WCST_TE ($F(1,43) = 7.34, p < .001$); education and StroopUE ($F(7,37) = 5.07, p < .001$) and with IGT40 ($F(7,37) = 3.45, p < .001$); professional categories and WCST_TE ($F(6,38) = 2.37, p < .05$) (table S7 and S8, S9).

Relation between measures of frontal functions and demographic variables in patients' group was examined using chi-square test of independence (table S4).

TABLE 1.

3.2. Factor analysis

The frontal lobe functions approach proposed by Stuss and Alexander (2007; Stuss, 2008, 2011, 2017), is based on the measure of 5 components. A factor analysis was then computed with 5 factors subjected to a varimax rotation. We found an explained variance of 96.98 % for the 5 first factors (see plot of the cumulative variance in the supplementary data) which is highly consistent with the 5 components described by Stuss and Alexander (2007; Stuss, 2008, 2011, 2017). Then, most of the maximum loading of each item was found on the predicted factor. EFs Monitoring items (WCST_SL, WCST_CA and WCST_TE) loaded more on Factor 1, B/E Self-functions (IGT_40, IGT_60, IGT_80, IGT_100 and IGT_NS) items on Factor 2, Metacognitive functions items (FauxPasGS, FauxPasCS and FauxPasAS) on Factor 3, Energization items (VF0_15, VF60_15 and VFT) on Factor 4, and EFs Task setting items (StroopTPS & StroopUE) on Factor 5. Absolute values greater than 0.40 are usually interpreted as high loadings (Tabachnick & Fidell, 2014). The maximum loading of each item was greater than 0.40, except for IGT_20, which is loading in none of the five factors (Figure 1). Thus, the original clustering of items in five factors, as proposed by Stuss and Alexander (2002), was found in our population (controls and patients with schizophrenia).

FIGURE 1.

3.3. Comparison between groups of controls and patients

In regard to primary analysis (see supplementary materials), Mann-Whitney U test for independent samples or Student t test were used to compare the control and patients with schizophrenia groups. As exposed in table 2, there is significant and large size difference between patients and controls groups, on two measures which refer to Energization. On the Phonemic Verbal Fluency task, the patient group produced fewer words in two minutes (VFT ($t(98) = -6.90, p < .0028; \text{Cohen's } d = 1.39$)) and fewer words in the 15 first seconds (VFT_15 ($U = 426, p < .0028; r = 0.57$)). The measure of the number of words given from 15 seconds to 60 did not show significant differences between the two groups (VF60_15 ($t(98) = -1.8, p = .06; \text{Cohen's } d = 0.36$)). There are significant and medium size differences between patient and control groups on all measures which refer to EFs (Task setting and Monitoring). There are significant and small size differences between patients and control groups, on two measures which refer to B/E Self-functions. After Bonferroni correction for multiple comparisons the results from the comparison of card choices from advantageous decks and disadvantageous decks (IGT_20; IGT_40; IGT_60; IGT_80; IGT_100 and IGT_NS) did not show significant differences between the two groups (table 2). All the measures which refer to Metacognitive functions have shown significant differences between the two groups. The understanding is better in the control group but the size difference is small (FauxPasGS($U = 880.5, p < .01; r = 0.29$)) and none of them scored below the centile 5 (Boutantin et al., 2010).

TABLE 2.

3.4. Correlation between frontal lobe functions in patient group.

The Spearman's correlation coefficient was used to examine the size and direction of the monotonic relationship on variables in patient group which differs significantly to the control group.

All the correlations are highly significant between each measure within each frontal function. Correlation between measures of Energization is positive and strong, such as VF0_15 correlate with

VFT ($\rho = 0.73$; $p < .001$). All the correlations between measures of EFs Monitoring functions are significant, Correlation between measures of EFs Task setting is positive and moderate, such as StroopTPS correlate with StroopUE ($\rho = 0.43$; $p < .001$). All the correlations between measures of Metacognitive functions are also significant, All the correlations between measures of B/E Self-functions are positive and strong, such as IGT_60 correlate with IGT_80 ($\rho = 0.63$; $p < .001$).

There are significant correlations between different measures of frontal lobe functions. WCST_SL are weakly and positively correlated with StroopTPS ($\rho = 0.37$; $p \leq .05$); the higher the number of Set Loss increases, the longer the time in Stroop task (ING less CN condition) increases to. StroopTPS are also weakly and negatively correlated with WCST_CA ($\rho = -0.30$; $p \leq .05$); the more time increased in Stroop, the fewer number of categories in WCST are achieved. IGT_80 is correlated moderately and negatively with FauxPasAS ($\rho = -0.41$; $p < .001$); the fewer patients who drew cards from the advantageous decks in trials 4 in IGT, the higher the number of good answers of questions related to ToM Affective in Faux Pas task.

FIGURE 2.

3.5. Profiles of frontal lobe functions in patient group.

In order to keep the 5 frontal lobe functions (Energization, EFs Monitoring, EFs Task setting, B/E Self-functions and Metacognitive functions), K-mean clustering algorithm was performed over significant measures, before Bonferroni correction, and 3 clusters were identified within our patients' group. Cluster 1 is composed of 20 patients, cluster 2 of 18 patients and cluster 3 of 7 patients. To characterize those clusters, we analysed the mean z-scores that the patients obtained on each frontal function. Note that to average the z-scores of the measures inside the EFs Monitoring (cf. Negative correlations in figure 2), all the scores of this frontal function were indicated in absolute value (figure 3).

Comparing patients' mean scores with control group's mean scores, we see that in cluster 1, and patients' mean score have a difference close to 1 standard deviation in all functions.

In cluster 2, patients' mean score have a difference near to 2 standard deviations in Metacognitive functions ($z=-1.8$), inferior or equal to one standard deviation in Energization ($z=-1.2$) and EFs Monitoring ($z=0.9$), and are close to the mean scores of control group in EFs Task setting ($z=0.2$) and B/E Self-functions ($z=0.1$).

In cluster 3, patients' mean score have a difference of 4 standards deviations in EFs Task setting ($z=4$), near to 2 standard deviations in Energization ($z=-1.8$) and EFs Monitoring ($z=1.7$), inferior or equal to 1 standards deviation in Metacognitive functions ($z=-1$), and are close to the mean scores of control group in B/E Self-functions ($z=-0.5$).

For each of the Stuss's component, we compute One-Way ANOVA to analyse the difference between the 3 clusters. Significant differences were observed for EFs Task setting ($F(2,42) = 19.53$, $p < .001$) and B/E Self functions ($F(2,42) = 5.36$, $p < .01$) (table S6).

FIGURE 3.

4. Discussion

This study aimed to examine the specificities of EFs deficits in schizophrenia, through the application of the integrative model of frontal lobe functions developed by Stuss (2017). The exploratory factor analysis reveals that all the measures, except IGT_20, loaded on the 5 expected frontal functions described by Stuss (2017).

For patients with schizophrenia, we observed alterations in almost all the frontal functions. Inside each frontal function, correlations are observed between all the corresponding measures, while 5 measures, from different frontal functions, correlated with each other. In schizophrenia, executive functioning involves distinct process related to different frontal region. As written by Stuss and Alexander (2000) "there is no ghost in the mind machine", frontal functions are not governed by a single entity.

More precisely, patients with schizophrenia have worse performances than controls in all the measures of EFs Task setting, EFs Monitoring, Metacognition and in most of the measures of Energization and B/E Self-functions. Although, some measures do not show differences between groups. Energization (verbal fluency: VF60_15) and 4 measures of B/E Self-functions (IGT: IGT_20;

IGT_40, IGT_100 and IGT_NS) are not significantly impaired in the patient group. Indeed, in the verbal fluency task, patients evoked fewer words than controls (in the beginning and in the whole task), but do not show a slowdown during the task. A review of literature by Lemieux and Macloir (2017) recognize that the processing speed is an important cause of deficits in schizophrenia, but also identified increased differences between patients and controls in semantic fluency compared to phonemic fluency. After Bonferroni's correction, no significant difference between group were observed for IGT scores. A possible explanation of this result lies in the version of the IGT used. As observed in previous studies (Kim et al., 2009; Buelow, Barnhart, 2018), the use of computerized version, of IGT test, could help to highlight the contrasts in the speed of shift from disadvantageous decks to advantageous decks over time between our groups.

Stuss (2008) did not develop its model for patients with schizophrenia (Stuss et al., 1998; Henri-Bhargava et al., 2018). Hence, it is possible that its application requires some adaptations. An adaptation concerns the measure of Energization, where it is possible to change the duration of the first measure or use semantic fluency. In the same vein, B/E Self-functions could be measured with the last block in IGT with a computerized version. Although it is not yet available in French or adapted to European culture (the currency is the dollar).

As mentioned previously, three correlations were observed between five measures from different frontal functions. One measure of EFs Task setting is correlated to two measures of EFs Monitoring. Patients who are slower than controls at Stroop task have a great number of set loss and a low number of categories achieved in WCST. Moreover, in our factor analysis, StroopTPS and StroopUE presented the second higher loadings in the Factor 1 associated to the EFs component. Confirmatory Factory Analysis could be used to determine the best fit model of frontal measures in schizophrenia, such as the interdependency of the EFs Monitoring and EFs Task setting, or to redefine the measures of B/E Self-functions. We observed that IGT_20 did not load in any of the factors and other measures of this component were not significant in schizophrenia (see figure 1 and table S5). One measure B/E Self-functions (which involves the VMPFC) is negatively correlated to one measure of Metacognition functions (which involves the frontal pole). The more "bad decisions" patients' take in IGT (4th trial), the better their ToM Affective score is. In regard to its affective connection with amygdala and other

limbic regions, the implication of VMPFC in ToM and decision making have already been observed by Stuss et al. (2001). But this study was done before the definition of frontal lobe functions and its mean of measurement. By changing the paradigm and referring to a precise model, our study allows us to question the possible contribution but antagonist of ToM in decision-making.

Through the profile analysis of patients with schizophrenia, we described three clusters showing heterogeneous frontal functioning. Cluster 1 is composed of patients with a mean score measure of each function which presents roughly the same distance to the mean of control group (around one standard deviation). Only the score of Energization is slightly above one standard deviation. This group can be called “slightly homogenous impaired frontal”. All measure of the frontal lobe area SMPFC, left LPFC, right LPFC, VMPFC and polar frontal (Stuss, 2008, 2011) show a small but almost equal difference. Cluster 2 is composed of patients with a mean score of measure of Metacognition which are the farthest to the mean of control group. This group can be called “the metacognitive”. Although, this cluster mostly refers to the frontal pole measure, corresponding to “hot” cognition, it also involves smaller difference than the group control in Energization and EFs Monitoring (SMPFC and LPFC). Cluster 3 is composed of patients with a mean score of measure of EFs Task setting which is the farthest to the mean of control group. Then come the measure of Energization and EFs Monitoring which presents a remarkable distance. This group can be called “the cognitive” and refers to SMPFC and right and left LPFC. Cluster 1 and 2 present simultaneously impairment on “hot” and “cold” EFs aspects. Clusters 3 and 2 exhibit intrinsic heterogeneity with preservation of some frontal functions. Our findings are consistent with the recent study on social cognition where several profiles of social cognition have been observed, characterized by different degrees of functioning and non-systematic impairments in socials functions Etchepare et al. (2021). We also found the same heterogeneous functioning as described by Raffard and Bayard (2012) in their study about cold EFs. Beyond traditional distinction between "hot" and "cold" EFs these characteristics can be considered as applying to all frontal functions. This integrative approach could improve evaluation of EFs and the understanding of their links within neurocognition which has been observed in schizophrenia (Di Tella et al., 2020).

Our sample size remains moderate and does not allow us to perform a confirmatory analysis, in order to reduce the selection of tests to match the Stuss model (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017), which we discussed previously. Two other limits can be underlined.

The first limit is related to the difference of characteristics (gender, education and professional category) in our samples. Schizophrenia has a male prevalence, which explains that we mostly recruited males for our patient group. Besides, for our control group, recruitment was done on a voluntary basis, and we mostly recruited females. Schizophrenia is a disease that occurs in young adults, its impact on education is observed in our samples. This disease is recognized as a source of disability, unfortunately, people with disabilities often encounter difficulty to access employment. In France, the employment rate for people with schizophrenia is only of 11.5% despite their desire to access employment (Chéreau et al, 2021). Again, we observed this difference between the professional categories of our two groups. In schizophrenia, gender was described to have an influence on cognitive deficits (Zhang et al., 2017). Even though, we observed a difference between gender groups, no relation could be found between gender and frontal functions. The estimation of premorbid IQ doesn't differ between groups. As already observed in dementia, the f-NART is based on ability to correctly read words spelled irregularly and remain relatively preserved of cognitive deterioration (Mackinnon & Mulligan, 2005).

The Second limit concerns the lack of functional neuroimaging of the brain. We are aware that Stuss build his model from patients with neuroanatomical lesions (Stuss & Alexander, 2007, 2008). This study focuses on clinical measures (following Stuss' recommendations), which could be use in clinical practice. Functional neuroimaging was not possible in the context of our study, nevertheless, its use would make it possible to corroborate our observations on the neuroanatomical levels.

5. Conclusions

Finally, Stuss' model (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017), encompasses the evaluation of frontal lobe functions, which are all altered in schizophrenia. Five distinct frontal lobe functions can be observed, as described by Stuss (Stuss & Alexander, 2007; Stuss, 2008, 2011, 2017). There is a need to go beyond fractionated executive system, in regard to different profiles which have

been obtained. The model of Stuss (2017) allows accurate and specific measures of the frontal functions and observation of their heterogeneous expression in schizophrenia. Patients with schizophrenia do not have cold or hot EFs but different frontal shades of warm.

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Table 1. Demographic characteristics of the sample.

		Patients (N = 45)		Controls (N = 55)		X ²	p-value
		Measure	Range	Measure	Range		
Gender						4.98	.02
<i>Female</i>	[N, %]	16 (35.6)	–	33 (60.0%)	–		
<i>Male</i>	[N, %]	29 (64.4%)	–	22 (40.0%)	–		
Age	[mean, std]	32.0 (8.3)	19 – 50	35.2 (11.7)	18 – 55	36.979	.33
Number of years of education *	[mean, std]	11.7 (2.0)	9 – 17	13.9 (2.2)	9 – 20	26.12	.002
Professional Category						19.401	.003

<i>Craftsmen, merchants, managing directors</i>	[N, %]	1 (2.2%)	–	3 (5.5%)	–		
<i>Employees</i>	[N, %]	15 (33.3%)	–	18 (32.7%)	–		
<i>Executives, managers, intellectual professions</i>	[N, %]	1 (2.2%)	–	8 (14.5%)	–		
<i>Farmer</i>	[N, %]	1 (2.2%)	–	1 (1.8%)	–		
<i>Intermediates professions, administrative workers, technicians</i>	[N, %]	1 (2.2%)	–	11 (20.0%)	–		
<i>Other without professional activity**</i>	[N, %]	13 (28.9%)	–	10 (18.2%)	–		
<i>Workers</i>	[N, %]	13 (28.9%)	–	4 (7.3%)	–		
f-NART	[mean, std]	106.7 (7.9)	82.86 – 122.9	110.0 (6.2)	98.26 – 119.82	–	–
Premorbid IQ Level***						6.774	.07
<i>Borderline mentally retarded</i>	[N, %]	1 (2.2%)	–	–	–		
<i>High average</i>	[N, %]	31 (68.9%)	–	36 (65.5%)	–		
<i>Low average</i>	[N, %]	8 (17.8%)	–	4 (7.3%)	–		
<i>Superior</i>	[N, %]	5 (11.1%)	–	15 (27.3%)	–		

Notes: f-Nart: French National Reading Test.

*With regard to the current French system, Primary Studies (1 to 5 years), secondary school (5 to 9 years), high school (9 à 12), further studies (above 12 years).

**Including students.

*** In regard to Wechsler IQ curve (Wechsler, 2008).

Table 2. Comparison between patient and control groups on component of frontal lobe functions in regard to Stuss (Stuss and Alexander, 2007; Stuss, 2008, 2011, 2017).

Prefrontal functions	Measures	Patients (N = 45)		Controls (N = 55)		Stat. (p-value)	Effect size
		Mean (std)	Range	Mean (std)	Range		
Energization SMPFC	VFT	16.6 (5.7)	7 - 31	25.3 (5.7)	11 - 31	t(98) = -6.9 (0.0000)*	d = 1.39
	VF0_15	4.1 (1.9)	1 - 9	6.3 (1.9)	4 - 9	U = 426.0 (0.0000)*	r = 0.57
	VF60_15	2.3 (2.2)	-2 - 8	3.3 (2.2)	-4 - 8	t(98) = -1.8 (0.068)	d = 0.36
Executive Functions Monitoring Right LPFC	WCST_CA	4.6 (1.1)	2 - 6	5.3 (1.1)	3 - 6	U = 740.0 (0.0001)*	r = 0.36
	WCST_SL	1.1 (1.0)	0 - 4	0.5 (1.0)	0 - 4	U = 806.5 (0.0006)*	r = 0.32

	WCST_TE	7.4 (5.8)	0 - 22	4.1 (5.8)	0 - 22	U = 746.5 (0.0003)*	r = 0.34
Executive Functions Task setting Left LPFC	StroopTPS	54.1 (23.8)	16 - 129	37.1 (23.8)	9 - 129	U = 635.0 (0.0000)*	r = 0.42
	StroopUE	1.0 (1.8)	0 - 9	0.2 (1.8)	-1 - 9	U = 884.5 (0.0011)*	r = 0.31
Behavioural/Emotional Self-regulatory functions VMPFC	IGT_NS	17.5 (26.3)	-48 - 60	24.8 (26.3)	-14 - 60	t(98) = -1.6 (0.112)	d = 0.32
	IGT_20	-2.9 (5.0)	-12 - 8	-4.2 (5.0)	-20 - 8	t(98) = 1.3 (0.195)	d = 0.26
	IGT_40	4.0 (7.9)	-14 - 20	4.9 (7.9)	-7 - 20	U = 1190.5 (0.373)	r = 0.03
	IGT_60	5.5 (9.1)	-20 - 20	8.7 (9.1)	-14 - 20	U = 950.0 (0.023)	r = 0.2
	IGT_80	5.0 (9.0)	-16 - 20	9.3 (9.0)	-6 - 20	U = 889.5 (0.008)	r = 0.24
	IGT_100	5.7 (9.4)	-9 - 20	6.0 (9.4)	-14 - 20	U = 1197.5 (0.392)	r = 0.03
Metacognition functions Frontal pole	FauxPasGS	33.2 (11.0)	8 - 53	45.7 (11.0)	24 - 53	U = 448.0 (0.0000)*	r = 0.55
	FauxPasCS	5.8 (2.3)	1 - 10	7.8 (2.3)	3 - 10	U = 611.5 (0.0000)*	r = 0.44
	FauxPasAS	5.1 (2.0)	1 - 9	7.2 (2.0)	1 - 9	U = 550.0 (0.0000)*	r = 0.48
	FauxPasUS	39.0 (1.4)	34 - 40	39.6 (1.4)	36 - 40	U = 880.5 (0.0019)*	r = 0.29

Notes: VF0_15: Verbal Fluency 0-15; VF60_15: Verbal Fluency 60-15; VFT: Verbal Fluency Total; StroopUE: Stroop number of Uncorrected Errors; StroopTPS: Stroop Time (in seconde); WCST_CA: Wisconsin Card Sorting Test number of Categories Achieved; WCST_SL: number of Set Loss; WCST_TE: number Total of Errors; IGT_NS: Iowa Gambling Task Net Score, IGT_20: Iowa Gambling Task score block 1; IGT_40: score block 2, IGT_60: score block 3; IGT_80: score block 4, IGT_100: score block 5; FauxPasGS: Faux Pas Global Score; FauxPasCS: Faux Pas ToM Cognitive Score; FauxPasAS: Faux Pas ToM Affective Score; FauxPasUS: Faux Pas Understanding Score; IGT_NS: Iowa Gambling Task Net Score.

“*” is indicating the significant p-value after Bonferroni correction for multiple comparisons ($p < 0.0028$).

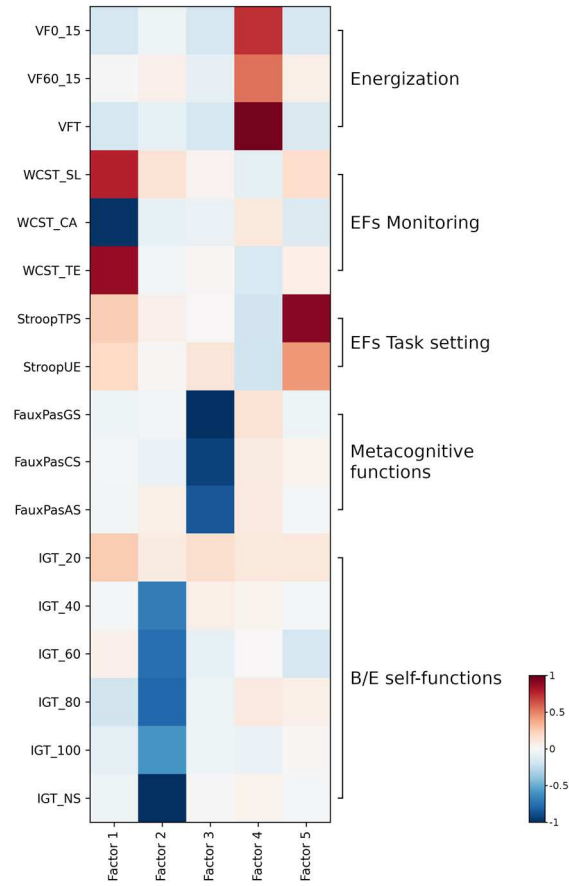


Figure 1. Loadings of the exploratory factor analysis. Cool colours indicate negative loadings and warm colours indicate positive loadings. Stuss and Alexander's components are indicated on the right of the figure.

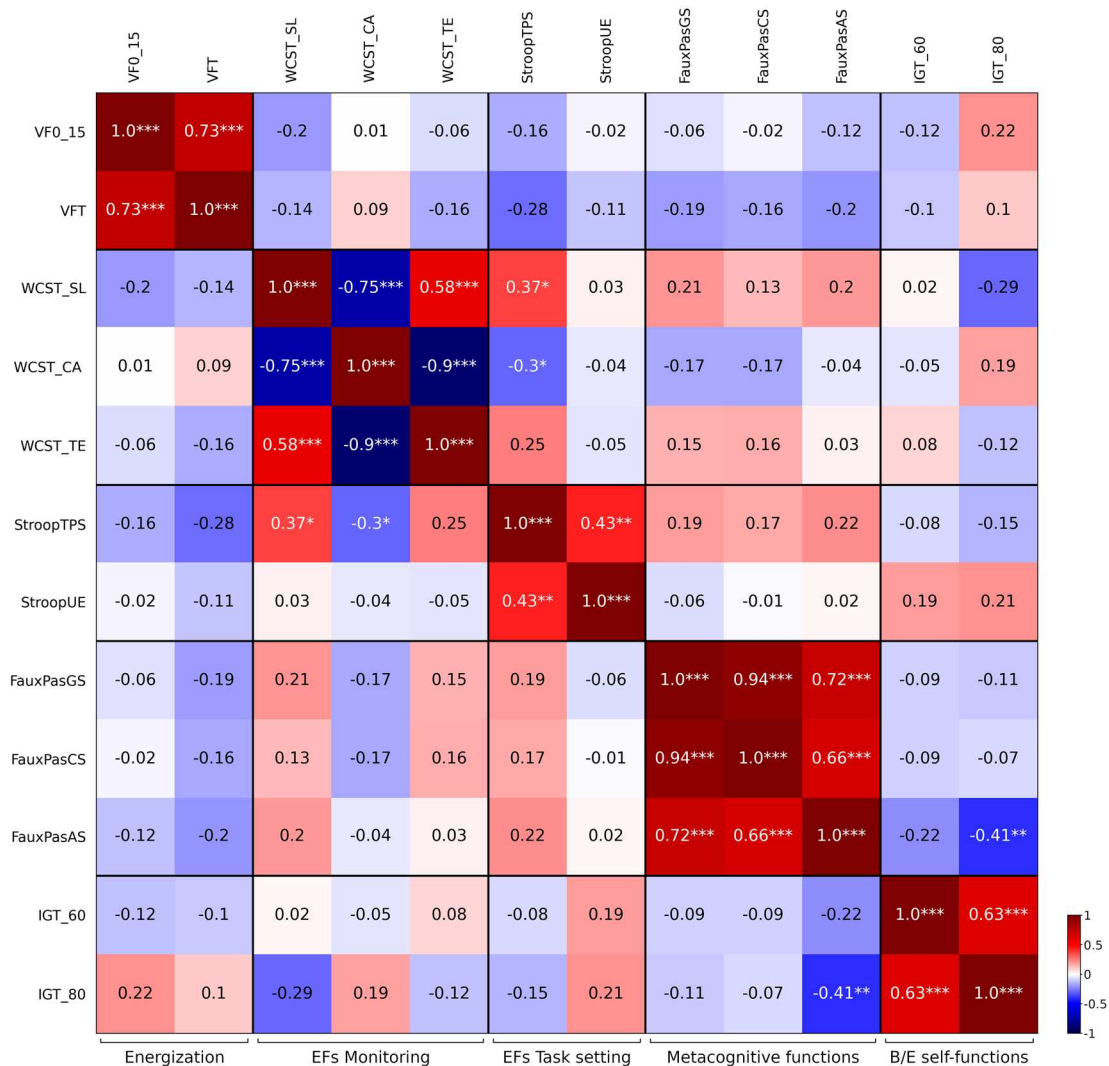


Figure 2. Correlation matrix of measures of frontal lobe functions in the patient group. Cool colours indicate negative correlations and warm colours indicate positive correlations. In addition to the colour scale, values of the correlations are indicated on the matrix and their p-value is indicated as follow: ***p<.001, **p<.01, *p<.05. Names of the measures is indicated on the matrix as follow: VF0_15: Verbal Fluency 0_15; VF60_15: VFT: Verbal Fluency Total; WCST_CA: Wisconsin Card Sorting Test number of Categories Achieved; WCST_SL: number of Set Loss; WCST_TE: number Total of Errors; StroopUE: Stroop number of Uncorrected Errors; StroopTPS: Stroop Time (in second); FauxPasGS: Faux Pas Global Score; FauxPasCS: Faux Pas ToM Cognitive Score; FauxPasAS: Faux Pas ToM Affective Score; IGT_60: score block 3; IGT_80: score block 4.

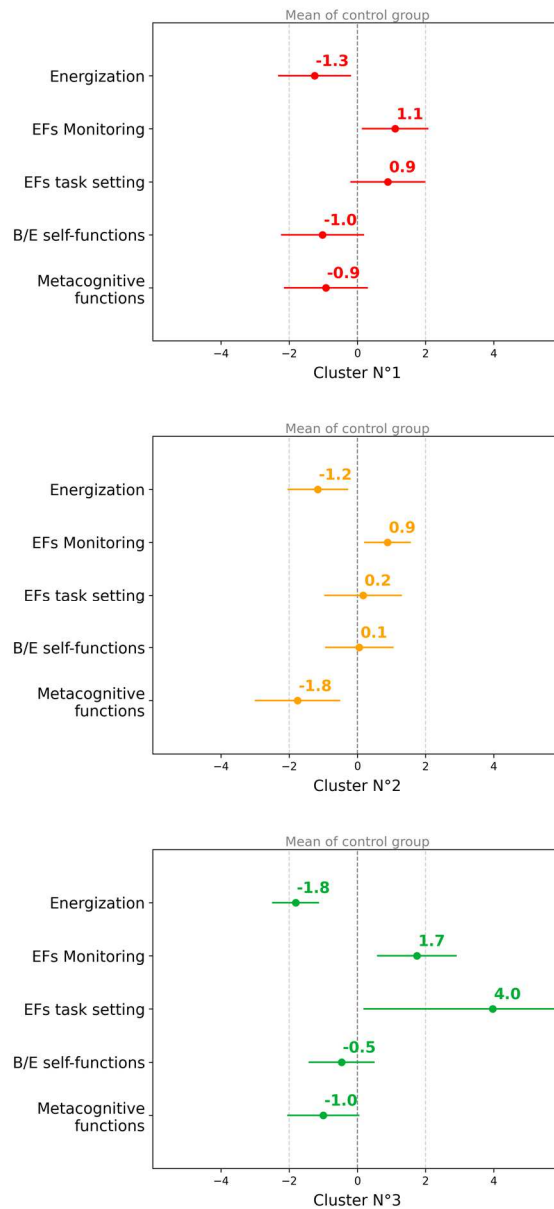


Figure 3. Profiling of frontal lobe functions in patients with schizophrenia. Plot of the z-score in frontal lobe functions of Stuss model (Stuss and Alexander, 2007; Stuss, 2008, 2011, 2017) (Energization, EFs Monitoring, EFs Task setting, B/E Self-functions, Metacognitive functions respectively) in each cluster. In each cluster, scores indicated on the graphs correspond to the mean z-scores of patients in each function. The dash lines at 0 indicate the mean of the controls; * The scores are indicated in absolutes in EFs Monitoring.